Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 34-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10, 34, and 35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/09*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 10/6/09 in response to the Office Action of 4/6/09 are acknowledged and have been entered.

Claims 36-40 have been added by Applicant.

Claims 1-7, 10, 34, and 35-40 are pending.

Claims 1, 34, and 35 have been amended by Applicant.

Claims 1-7, 10, 34, and 35-40 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by amendments requiring detection of MAGE-A3 and/or PAX3 mRNA.

The Interview of 9/17/09

During the interview of 9/17/09, the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) were discussed. In the Reply of 10/6/09, Applicant indicates that a new rejection under 35 U.S.C. 103(a) may have been set-forth during the interview. In response, there was not a new rejection under 35 U.S.C. 103(a) set-forth by the Examiner in the interview of 9/17/09.

Rejections Withdrawn

All previous rejections are withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-7, 10, 34-36, and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826).

Hoon et al teaches a method of detecting circulating melanoma cells comprising: (a) isolating nucleic acid from a sentinel lymph node (SLN) sample, tumor draining lymph node sample, or blood sample obtained from a melanoma patient; (b) amplifying mRNA transcripts encoded by GalNAcT, MAGE-3, and MART-1 marker genes from the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient wherein amplification is done by PCR; (c) detecting

the levels of GalNAcT, MAGE-3, and MART-1 mRNA transcripts in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient; and (d) comparing levels of the mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in nucleic acid from a SLN, tumor draining lymph node sample, or blood sample obtained from a second melanoma patient to levels of mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the first melanoma patient to determine melanoma status (see lines 15-19 of column 3, claim 69, and lines 57-59 of column 41, in particular), assigning a clinical melanoma stage to the subject (column 38 lines 45-51 and column 40 lines 4-6, in particular), predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). it is noted that "MAGE-3" is an alternate name of "MAGE-A3" as recited in the instant claims. The method taught by Hoon et al further comprises predicting melanoma recurrence or survival of the subject for a period of greater than 30 months following removal of a primary tumor, SLND, or both (Figure 1, in particular). The method taught by Hoon et al further comprises samples wherein the histopathology of the body fluid or tissue sample is determined by H&E and would determine whether the SLN or blood sample from the subject is histopathologically positive of negative for melanoma cells (Example VII, in particular). Hoon et al further teaches a method wherein a high number of genes expressed indicates an advanced

melanoma stage, progression or melanoma, a high probability of melanoma recurrence, or a low probability of survival (Figure 1, in particular). Hoon et al further teaches a method wherein the samples are frozen (see Example VII, in particular). In the method of Hoon et al, the detection of GalNac-T, MAGE-3, and MART-1 in a sample from a subject, as compared to a subject without detected GalNac-T, MAGE-3, and MART-1, correlates with melanoma recurrence and shorter relapse-free survival because detection indicates the presence of circulating melanoma cells. Further, the abstract of Hoon et al states "Methods using multiple markers provide increased sensitivity over existing methods" and Example XIII of Hoon et al states "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, subjects expressing a higher number of melanoma-specific markers (such as GalNac-T, MAGE-3, and MART-1) in samples would be expected to be worse off than patients expressing a lower number of melanoma-specific markers because those expressing a lower number of melanoma-specific markers would include those that express no markers, as well as false-positive results, and subjects with a higher number of melanoma-specific markers would more accurately detect circulating melanoma cells in subjects that have a higher likelihood of recurrence and shorter relapse-free survival as compared to patients expressing a lower number of melanoma-specific markers which do not have circulating melanoma cells.

Hoon et al does not specifically teach PAX-3 being part of the panel of genes used. However, this deficiency is rendered obvious or made up in the teachings of Scholl et al.

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX-3 and MAGE-A3, and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting and characterizing metastatic melanoma as taught by Hoon et al with a panel of genes comprising PAX-3 because Hoon et al teaches incorporating nucleic acids of any melanoma markers into the panel (see column 3 line 9-14, in particular) and Scholl et al teaches PAX-3 nucleic acid is a melanoma marker (see Table 1 and Table 2 of Scholl et al, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when performing the method taught by Hoon et al with a panel of genes comprising PAX-3 because Scholl et al has demonstrated that PAX-3 nucleic acid is a marker of metastatic melanoma (see Table 1 and Table 2 of Scholl et al, in particular). Further, Scholl et al teaches PAX-3 and MAGE-A3 are overexpressed in metastatic malignant melanoma cells in vivo (pages 825-826, in particular) and Hoon et al teaches GalNAc-T, MAGE-A3 (MAGE-3), and MART-1 are also overexpressed in metastatic melanoma cells in vivo (column 2 line 53 to column 3 line 36, lines 15-20 of

column 3, and Example IV, in particular). Since Scholl et al and Hoon et al teach overlapping panels of genes that are overexpressed in the same type of sample (metastatic melanoma cells) and Hoon et al teaches metastatic melanoma cells would be detected in body fluid samples (column 2 line 53 to column 3 line 36 and Example IV, in particular), one of skill in the art would expect PAX-3 to be overexpressed by metastatic melanoma cells in body fluid comprising metastatic melanoma cells. Further, one of skill would expect said melanoma recurrence and survival would be predicted for a period of at least three years following removal of a primary tumor, SLND, or both by detecting GalNAc-T, MAGE-A3, and MART-1 because Hoon et al teaches said melanoma recurrence and survival would be predicted for a period of at least 30 months following removal of a primary tumor, SLND, or both by detecting multiple markers of circulating melanoma cells including MAGE-A3 (Figure 1, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 10/6/09, Applicant argues that Hoon does not utilize techniques for quantifying the levels of RNA in the samples because qPCR is not utilized by Hoon et al. Applicant further indicates that the instant claims differ from published techniques because quantitative nature of each assay point of the instant invention is based on a standard curve of known copy number of the same gene cDNA. Applicant further argues that Hoon fails to provide a step of comparing levels of mRNA transcripts to predict metastatic melanoma recurrence, metastatic melanoma-free survival, overall survival, or a combination thereof as claimed.

The amendments to the claims and the arguments found in the Reply of 10/6/09 have been carefully considered, but are not deemed persuasive. In regards to the argument that Hoon does not utilize techniques for quantifying the levels of RNA in the samples because qPCR is not utilized by Hoon et al, only instant claims 4 and 37 require qPCR. Further, Johansson et al (2000, Clinical Chemistry, 46(7): 921-927) teaches a reproducible method comprising performing qRT to quantitatively detect mRNA markers of melanoma in blood samples (see rejection below).

In regards to the argument that the instant claims differ from published techniques because quantitative nature of each assay point of the instant invention is based on a standard curve of known copy number of the same gene cDNA, Applicant is arguing limitations not recited in the instant claims. The instant claims do not require an assay point based on a standard curve of known copy number of the same gene cDNA.

In regards to the argument that Hoon fails to provide a step of comparing levels of mRNA transcripts to predict metastatic melanoma recurrence, metastatic melanoma-free survival, overall survival, or a combination thereof as claimed, Hoon et al teaches methods of determining melanoma status (see lines 15-19 of column 3 and lines 57-59 of column 41, in particular), assigning a clinical melanoma stage to the subject (column 38 lines 45-51 and column 40 lines 4-6, in particular), predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). Further, as illustrated in Figure 1 of Hoon et al, when performing the method of Hoon et al, a comparison of levels in

samples is made between sample that express markers and samples that do not express markers.

Claims 1-7, 10, 34-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826) as applied to claims 1-3, 5-7, 10, 34-36, and 38-40 above, and further in view of Johansson et al (2000, Clinical Chemistry, 46(7): 921-927).

Teaching of claims 1-3, 5-7, 10, 34-36, and 38-40 by Hoon et al in view of Scholl et al is discussed above.

The combined teachings of Hoon et al and Scholl et al do no specifically teach using qRT-PCR to detect PAX3, MAGE-A3, and GalNacT expression. However, these deficiencies are made up in the teachings of Johansson et al.

Johansson et al teaches a reproducible method comprising performing qRT to quantitatively detect mRNA markers of melanoma in blood samples (pages 922-923, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use qRT to detect expression of marker genes when performing the method of detecting and characterizing metastatic melanoma as taught by the combined teachings of Hoon et al and Scholl et al because qRT is a quantitative method of detecting specific mRNA transcripts (Figure 4 of Johansson et al, in particular) which would streamline the method and facilitate comparison between multiple experiments and remove discrepancies relying on visual inspection of an

electrophoresis gel (see Hoon et al at lines 13-14 of column 17, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when using qRT to detect expression of marker genes when performing the method taught by the combined teachings of Hoon et al and Scholl et al because Johansson et al demonstrates that qRT quantitatively detects transcripts which are mRNA markers of melanoma in body fluid samples (pages 922-923, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 10/6/09, Applicant argues that Hoon does not utilize techniques for quantifying the levels of RNA in the samples because qPCR is not utilized by Hoon et al. Applicant further indicates that the instant claims differ from published techniques because quantitative nature of each assay point of the instant invention is based on a standard curve of known copy number of the same gene cDNA. Applicant further argues that Hoon fails to provide a step of comparing levels of mRNA transcripts to predict metastatic melanoma recurrence, metastatic melanoma-free survival, overall survival, or a combination thereof as claimed.

The amendments to the claims and the arguments found in the Reply of 10/6/09 have been carefully considered, but are not deemed persuasive. In regards to the argument that Hoon does not utilize techniques for quantifying the levels of RNA in the samples because qPCR is not utilized by Hoon et al, only instant claims 4 and 37 require qPCR. Further, Johansson et al teaches a reproducible method comprising

performing qRT to quantitatively detect mRNA markers of melanoma in blood samples (pages 922-923, in particular).

In regards to the argument that the instant claims differ from published techniques because quantitative nature of each assay point of the instant invention is based on a standard curve of known copy number of the same gene cDNA, Applicant is arguing limitations not recited in the instant claims. The instant claims do not require an assay point based on a standard curve of known copy number of the same gene cDNA.

In regards to the argument that Hoon fails to provide a step of comparing levels of mRNA transcripts to predict metastatic melanoma recurrence, metastatic melanoma-free survival, overall survival, or a combination thereof as claimed, Hoon et al teaches methods of determining melanoma status (see lines 15-19 of column 3 and lines 57-59 of column 41, in particular), assigning a clinical melanoma stage to the subject (column 38 lines 45-51 and column 40 lines 4-6, in particular), predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). Further, as illustrated in Figure 1 of Hoon et al, when performing the method of Hoon et al, a comparison of levels in samples is made between samples that express markers and samples that do not express markers.

Summary

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642